Peptic ulcer disease: a critical analysis of the current state of the problem

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Key words: peptic ulcer, history of research, Helicobacter pylori, pathogenesis, clinical picture, treatment

The more conscious the doctor's conclusion is when the patient is in bed, the more scientific it will be.
S.P. Botkin

Back in 1970, the outstanding Russian clinician and scientist V.H. Vasilenko (1897–1987) in his well-known article "What we do not know about a peptic ulcer (ways to study the problem" [1]) outlined his concept of the origin and course of peptic ulcer (PU), summarizing the facts known to science by that time and giving its prediction further development of this problem for years and decades ahead.

V.H. Vasilenko proposed the following definition (definition) of PU: "PU should be understood as a chronic recurrent disease characterized by a common morphological feature — loss of a mucous membrane area in those areas of the digestive tract that are more or less washed by active gastric juice" [1], adding: "The old position advanced by the Austrian surgeon K. Schwartz in 1910: "There is no ulcer without acid" remains in force " [1, 20, 47].

In our opinion, the following words should be considered as a key reflection of his views on PU: "An ulcer is a local expression of some general violations" [1]. The same provision was the basis of the recommendation of M.P. Konchalovsky called this disease "peptic ulcer disease", thus emphasizing that this is not a local pathological process in the mucous membrane of the

gastroduodenal zone, but a common disease of the whole organism [8].

A brief history of the teachings of PU. Since the first description of PU (1830–1842) by J. Cruveilhier passed over 180 years. Already at that time, speaking of the origin of peptic ulcer, he wrote: “The causes of the formation of a “round stomach ulcer” are covered with a veil (“darkness”) of uncertainty” [41].

In 1949, M.M. Gubergrits speaking at the All-Union Congress of Therapists, called PU a “mysterious stranger,” meaning the mysterious stranger from the poem of the same name, A.A. Block [4]. And after another 20 years (in 1969) O.S. Radbil, continuing the same imaginative series, wrote: "We lifted the veil, but have not yet looked into the face of the stranger" [12].

The above literary reminiscences vividly reflect the dissatisfaction of scientists of that time with knowledge about the origin of PU.

Throughout the long history of studying ulcer, numerous scientists in various countries have proposed hypotheses (theories) of the mechanism of development (pathogenesis) of ulcer. So, at different times were proposed: vascular theory (Virchow R., 1852); peptic (Bernard K., 1856; Quinke H., 1882); mechanical (Aschoff L., 1912); neuro-reflex (Rossle R., 1913); inflammatory gastritis (Konjetzny G. 1923); psychosomatic (Alexander F., neurotrophic me (Speransky A.D., 1935); Tyco armature-visceral (Bykov K.M., Kurtsin I.T., 1949); violations of the mucous-bicarbonate barrier (Hollander F., 1954); neurohumoral (Bojanowicz K., 1963); immune (Grinberg O.Y., 1966) and others.

V.H. Vasilenko called all these theories "Noah’s Ark", which can never reach a peaceful harbor [1]. After analyzing all these theories, he came to a disappointing conclusion: “There is not a single theory of PU, not a single approach to its prevention and treatment” [1, 20].

In 1983, Australian scientists J.R. Warren and B.J. Marshall discovered in the stomach a previously unknown bacterium, later named Helicobacter pylori (Hp); most often it was detected in the

stomach in patients with chronic gastritis (CG) and ulcer [49]. Soon they began to assert that it is Hp that is the main cause (etiological factor) of PU. Thus, an infectious conception of the origin of PU was formed, which, unfortunately, still dominates, despite the fact that the facts multiply each year disprove it.

Hp infection. The study of Hp over the past 30 years after its discovery has allowed us to establish the following facts (briefly).

1. Hp is a non-invasive bacterium whose activity is limited to the gastric compartment; neither on the stratified squamous epithelium of the esophagus, nor on the cylindrical epithelium of the intestine, including the duodenum (duodenum), it cannot exist, with the exception of foci of gastric metaplasia in these organs.

2. Hp is a microaerophilic, spiral-shaped bacterium that has at its one end 4 — 5 flagella, allowing it to move in the layer of mucus in the gastric supraepithelial search for the existence of optimal conditions (pH, osmolarity, etc.).

3. Hp colonize only the layer of supepithelial mucus; the outer surface of the gastric epithelium (between the villi) and (partially) the intercellular space. Neither in the subepithelial space, nor in the epithelium of the gastric glands, as a rule, they are not found.

4. Hp-infection is widespread on all continents of the globe and in all ethnic groups of the population, including those in the developed countries of Western Europe and North America — in 35 — 50%, and in developing countries in Asia, Africa and Latin America — 90 — 95% ; on average, in 60% of the population of our planet [7, 35].

5. In the later stages of evolution, part of Hp acquired an pathogenicity-associated island (PAI) as a result of horizontal transmission from some other microbe, located on the chromosomal DNA region [7, 14]. The “pathogenicity island” contains cytotoxicity genes — CagA, VacA, IceA, BabA, and the “island” marker is the immunodominant cytotoxin (protein) CagA (cytotoxin — associated gene A) encoded by the cagA gene [7].

At the same time, it was not possible to establish the connection of cytotoxic Hp strains with a specific gastroduodenal

disease (PU, GC, CG): "ulcerogenic", "carcinogenic", etc. Hp strains does not exist. Furthermore, qi totoksicheskie Hp strains are found not only at PU (in 59–91%), but also in other diseases unrelated c Hp-infection: when a functional syndrome (gastroduodenal) dyspepsia (SFD) — 46% and even healthy s-bacillicarriers — 27%, without causing them any harm [7, 21].

6. During antibacterial therapy with the use of broad-spectrum antibiotics, part of Hp dies, and part of it is transformed from a spiral form (helical — like) to coccoid (coccoid — like), in which the metabolism is sharply reduced and reproductive capacity is lost, but resistance to adverse environmental factors. At the same time, the coccoid forms of Hp retain the potential for reversion (reverse transition to a spiral shape) with favorable shifts in their environment [7].

7. The main reservoir of Hp infection is man himself, and the main route of infection is fecal-oral. In the external environment (soil, water) to detect Hp is still not possible.

8. Approximately 70% of people infected with Hp, — it is healthy bacillicarriers often lifelong. And various gastroduodenal diseases develop in less than 1% of those infected with Hp [7, p. 68]. These facts served as a basis for the well-known Russian microbiologist S.V. Sidorenko to state: “The widespread distribution of Hp infections among people without signs of pathology is a weighty argument that disproves the leading role of Helicobacter pylori in the development of gastroduodenal diseases” [14].

Hp is characterized by a special tendency to variability — genetic polymorphism, in connection with which they are often referred to as "chameleon" [7].

9. Hp are among the potentially pathogenic bacteria, but most often they do not show their virulence. Renowned gastroenterologist M.J. Blaser (USA) says: “Depending on the specific circumstances, Hp can behave like commensals (commensal — French — “companion”), or even as symbionts,

being a component of the normal microflora of the stomach, but under certain conditions can also act as pathogen" [37, 38].

Addressing the Gastronedele USA (2014), M.J. Blaser eloquently called his report: " Helicobacter pylori: friend or foe? "

10. Among the factors of pathogenicity of Hp should be called their ability to form the enzyme urease, which acts as a toxin that damages the gastric epithelium. Urease contributes to the development of the inflammatory process in the stomach (CG) due to the activation of neutrophils and monocytes, the stimulation of pro-inflammatory cytokines, the activation of free radical lipid oxidation (FRLO) and the synthesis of nitric oxide (NO).

In Hp revealed several adhesins that interact with the epithelium of the stomach, such as a cytotoxin BabA (Blood — group associated binding adhesin), promotes adhesion of bacteria to epithelial cells. VacA cytotoxin (vacuolating — associated cytotoxin A) causes vacuolation of cells with the formation of ion-selective channels in them. However, this ability is inherent in only 50% Hp containing VacA [7]. IceA cytotoxin (induced by conding adhezin)) has 2 alleles — IceA 1 and IceA 2. The IceA 1 allele is believed to promote inflammatory infiltration of the gastric mucosa (LCL) by polymorphonuclear neutrophils [1].

In certain circumstances, Hp may lose the "island of pathogenicity" and virulent properties [7].

It is important to note that, for example, in Southeast Asia, as established by a specially conducted study, about 90% of those infected with Hp who determined the virulent strains of this bacterium were healthy bacteria carriers [40].

Etiology of PU. American gastroenterologist D.Y. Graham gained fame mainly as the author of the postulates (provisions taken without evidence): "No Hp — no PU"; "Good" Hp — only dead Hp"; "Hp is a pathogenic microorganism that serves as the main cause of PU"; "Eradication of Hp leads to complete cure of PU"; "PU goes down in history" and others [42]. It should be immediately noted that none of the above postulates found its confirmation.

1. For recognition of a microorganism (bacteria, virus) as the etiological factor of the disease, it is necessary, as is well known, that it meets three conditions (requirements) of R. Koch. However, Hp, as the alleged cause of PU, does not correspond to two of them: a) the microbe-causative agent of the disease (Hp), isolated in a pure culture, when administered to a person susceptible to it should cause the development of the disease (PU).

One of the "explorers" Hp B.J. Marshall showed a certain courage by introducing into the stomach a concentrated suspension of pure Hp culture (10 9 microbial bodies). After 7 — 10 days, he developed the typical clinical picture of acute gastritis, not ulcer, which soon disappeared without any consequences. Other volunteers, who repeated the experiment with self-infection with the Hp culture, obtained a similar result [44].

Outstanding Russian pathologist I.V. Davydovskiy argued: "The reason that does not work, is not at all the reason" [5].

2. The second requirement of the “Koch triad” says: the microbe, the causative agent of the disease (in this case, Hp) must always be found in a patient with PU. As it turned out, a large proportion of cases ulcer develops without the participation of Hp, — the so-called Hp -negative forms of PU, in which the use of even 2–3 methods of identifying Hp does not detect their presence. It is now established that the Hp-negative form of PU range from 20 — 30% to 50% of all cases. Thus, in the US, Hp-negative forms of PU occur with a frequency of 39% (Schubert et al., 1999) up to 52% (Sprung et al., 1997), and in Australia — 45% (Henry et al., 1998) [7, p. 106].

In connection with the establishment of the possible existence of Hp-negative (idiopathic) forms PU categorical postulate D.Y. Graham “No Hp — No PU” was acknowledged as erroneous and was replaced with a more correct one: “No Hp — no Hp-associated PU” [48], recognizing the existence of Hp- negative forms of PU.

3. Supporters of the etiological role of Hp in ulcer disease stated that Hp in the stomach has no competitors, and in cases of

detection of another microflora, it was declared transitory, unable to colonize the coolant [7].

To check the accuracy of this statement, we conducted a study of the bacterial composition of the stomach in patients with ulcer using modern methods of microbiological research (in collaboration with a microbiologist — Y. Zakharova, MD).

We examined 42 patients with PUD of the stomach and duodenum. The average age of the examined was 52.9±3.8 years, including 57.1% of men and 42.9% of women. The diagnosis of ulcer was established on the basis of a comprehensive clinical, laboratory and instrumental examination (history, clinic, gastroduodenofibroscopy — GDFS with targeted multi-point biopsy with sterile gastroscope forceps and subsequent histological, cytological and microbiological research of biopsy material). Before GDFS, the patient's oral cavity was treated with an antiseptic. The biopsy material was obtained primarily from the periuserotic zone ("inflammatory roller"). Digital data was processed using Biostat for Windows, version 4-03, and Excel tables Windows Microsoft.

In PU, the growth of microflora was obtained in 90.5% of cases, including in the form of microbial associations, in 69.4%. Total of biologics coolant and duodenal ulcer at 93 been allocated but a different bacterial strain. Most often in patients with ulcer met: Streptococcus spp. — 57.1% at a concentration of 3.1 lg CFU/g; Staphylococcus spp. — 23.8% at a concentration of 2.2 lg CFU/g; mushrooms of the genus Candida spp. — 40.5% (1.5 lg CFU/g); Corynebacteriurn spp. and Neisseria spp. — no 7.1% (2.3 and 4.3 lg KOE/r). Hp were isolated in 52.4% (3.0 lg CFU/g). In addition, the following were determined: Enterobacteriaceae spp. — 9.5% (3.8 lg CFU/g) and more. etc. The highest degree of concentration is noted: in Haemophilus spp. (5.0 lg cfu/g) and Neisseria spp. — (4.3 lg cfu/g). On average, the concentration of microbial cells in the perioluse zone in ulcer patients was 2.7 lg CFU/g, i.e. turned out to be low.

When studying the virulent properties of the isolated microbiota, 27.3±6.0% of their urease activity was established, 36.6±-6.5% — the presence of pathogenic properties natural or acquired in the process of adaptation to the aggressive environment of the stomach; 45.5±6.7% — resistance to the action of various antibacterial agents used for the eradication of Hp. In general, signs of pathogenicity were determined in 56.4±6.7% of isolated microorganism strains [27].

Thus, the microbial landscape of the stomach is characterized not by helicobacteriosis, but by dysbacteriosis, and the selected bacteria are not transient, but mucosal microflora (M-microflora), which has adhesiveness, and in a considerable part of cases — invasiveness (unlike Hp) and pathogenic properties, and, therefore, the ability to determine the development of inflammatory -erosive-ulcerative lesions of the stomach and duodenum, along with Hp and independently of them [2, 22, 23].

Furthermore, it should be noted that the effectiveness of eradication therapy cannot serve as evidence of the exceptional role of Hp in the development of the disease, since this destroys all bacterial microflora colonizing the stomach, and not just Hp [22, 23, 27].

4. The infectious concept of origin of Hp can't explain why if there is Hp in the stomach, the ulcer spontaneously cicatrizes without any treatment in 4–5 weeks? Why when infected with Hp stomach forms a usually solitary ulcer, not multiple erosive and ulcerative lesions, and for ulcer is characterized by a change of relapses and remissions?

Refutes the etiological role of Hp in PU and the absence of significant positive changes in its prevalence in the world. So, recently one of the most convinced adherents of infectious (Hp) concept of the origin of PU (IV Mayev) in an article devoted to current trends in the study of diseases of the stomach and duodenum, was forced to admit: "Despite the already many years of active struggle with... Helicobacter pylori — infection, the prevalence of peptic ulcer in our country and in most countries of

the world is not reduced; the frequency of its terrible complications (bleeding, penetration, perforation) remains stable high (at the level of 10%) [10].

Consequently, active antibacterial therapy for the past 20 years, aimed at destroying Hp and curing PU, was unsuccessful!

Even such a well-known supporter of the leading role of Hp in the origin of gastroduodenal diseases, like V.A. Isakov (leading author of the famous monograph "Helicobacteriosis". — Moscow, 2003) in his doctoral dissertation on PU ("YDK associated with Hp: Diagnostics, pathogenesis, treatment." M., 2000) confirms: "Prove an etiological the role of Hp in PU is not yet successful".

The above undisputed scientific facts and arguments give the remaining grounds to consider PU as an idiopathic, rather than an infectious disease, the ethology of which is still unknown [21, 22, 23].

According to M. J. Blaser, "There is a certain balance between the negative and positive effects of Hp on a person" [1].

Pathogenesis of PU. For nearly half a century we have been studying the pathogenesis of PU, viewing it as a systemic disease with multiple and complex mechanism of development — as opposed to infectious concept, which believes that the ulcer — is a local process that develops in the stomach and duodenum due to their contamination Hp (D.Y. Grahan: "Peptic ulcer should be seen as a local manifestation of a bacterial infection — Hp") [10].

We believe that the following are involved in the pathogenesis of ulcer: genetic factors (heredity burdened by ulcer); psycho-emotional and psychosocial stress; immune disorders; in egetativnaya dysfunction; oxide tive stress, etc.

1. Inherited predisposition to PU is transmitted in an autosomal recessive manner. Cases of the familial ulcerative process were described when PU suffered from 5 generations of the same family, or the mother and her four sons born in two marriages were ill, as well as both identical (monozygous) twins [28].

Among the markers of hereditary predisposition to ulcer can be called: hyperpepsinogenemia-1 (the risk increases 5 — 8 times);

deficiency of alpha 1 antitrypsin (1.4-3 times); an increase in the mass of the occipital cells of the gastric glands (from 10–15 to 40%); a particular blood type phenotype (according to Levis); “Non-secretory status” (inability to excrete AVH system blood agglutinogens with saliva); features dermatoglyphics on the palms of the hands; the presence of certain histocompatibility antigens of the HLA system (B_5, B_{10}, B_{35}) is an immunogenetic factor, etc. [3, 31, 46].

Genetic determinism to PU occurs only after reaching the critical number (threshold accumulation) combined hereditary traits and AUC binds to an increased risk of ulcer and not fatal it inevitable. According to the model analysis, the development of PU is associated with genetic factors in 39% of cases (in the range from 32 to 47%) [3].

2. Immune mechanisms of PU pathogenesis. Having studied the immune status of patients with ulcer disease, we established the presence of a combined form of secondary immunodeficiency with preferential suppression of the T-cell immunity, as well as the ineffectiveness of microbial antigen disintegration in phagocytic cells [30].

3. An important role in the pathogenesis of ulcer belongs to psychogenic factors (psychoemotional, psychosocial stress; anxiety; mental disadaptation).

It is known that ulcer suffers only a person, and the number of patients with ulcer and its terrible complications (bleeding; ulceration to neighboring organs; perforation into the free abdominal cavity) increases many times during wars, economic depression, etc. [1, 23, 25, 26].

Stress states caused by adverse external influences serve as an important “triggering” factor in somatic disease (PU), disrupting the activity of the functional (regulatory) body systems. In this sense, PU with a particular base mo Jette be ranked to psychosomatic diseases in which increased activity emotiogenic zones limbic-reticular complex, referred to as "visceral brain", the

spread on the peripheral organs, including the stomach and duodenum.

We have found that in patients with a tendency to develop PU, even in their young age, interpersonal ties are disturbed, emotional deprivation is observed, which manifests itself in mature years by the inflexibility of responding to the demands placed on them, lack of competitive competition skills. In patients with ulcer disease, we identified the presence of various psychopathological disorders, including psycho-vegetative syndrome with the prevalence of asthenic-depressive symptoms [26].

The role of "disturbing factor" can be fulfilled by family and labor conflicts; sudden material problems, etc., and the choice of a "target organ" (stomach, duodenum) is determined by hereditary ulcer burden and the presence of ready-made biological determinants; the realization of psychosomatic illness is carried out with the participation of the personality factor [25].

In the personality structure of patients with ulcer we have established the predominance of cycloid and epileptoid traits; less often met emotive and demonstrative (emotionally unbalanced) types [25, 26].

It is important to emphasize that psychosomatic diseases develop in the organ or system of organs that appears to the patient most important in the functioning of the body. V.H. Vasilenko stated: "Some people "live with the heart" and suffer from angina pectoris and myocardial infarction; others — "live in the stomach" and are candidates for peptic ulcer disease" [1, 20].

4. Another factor in the pathogenesis of PU is the activation of free radical oxidation of lipids (oxidative stress). It was found that polymorphonuclear leukocytes generate reactive oxygen species, hydrolytic enzymes and bactericidal proteins. The mechanism of the damaging effect of SRLO products on cell membranes involves the inactivation of sulfhydryl groups (SG) enzymes, hormones and cell receptors, as well as the release of histamine by fat cells and the induction of various cellular mutations (geno- and cytotoxic effects) [18].

In an immunodeficient state, ischemia (hypoxia), an inflammatory process, including in patients with ulcer disease, excessive formation of SRLO products (diene conjugates, malonic dialdehyde, hydroperoxide) is observed. The control over the activity of SRLO processes is carried out by antioxidant protection factors with cytoprotective properties. However, in their functional insufficiency (depression), oxidative stress occurs, during which SRLO products "attack" cellular structures with damage to the lipids that make up the cell membranes, increasing their permeability and causing destruction of cells, thereby contributing to the formation of an ulcer in the stomach or duodenum [15, 18].

5. To the local pathogenesis factors of ulcer we include: a) disturbances of regional blood flow in the wall of the stomach and duodenum, arising from an increase in vascular tone, a decrease in arterial blood flow and venostasis [18]; b) an increase in gastric secretion and acidopeptic activity of the gastric juice; c) colonization of the stomach of Hp and other mucosal microflora [23].

And there must be mo noted that the increase in Acid opepticheskoy activity of gastric juice — it obbligato ny factor in the pathogenesis of PU ("no HCl — no ulce"), and contamination of the duodenum by Hp — optional, so the spacecraft to the ulcer may develop without any participation this bacterium (Hp -negative form of ulcer) [21, 23].

A long-term study of the problem of ulcer allowed us to develop and substantiate the original concept of pathogenesis and sanogenesis of ulcer [23, 29] and the concept of the relationship of Hp infection with the human body [13]. However, due to the limited length of the article, we could not include the presentation of these concepts in its text. Those interested in these problems, we refer to our publications of previous years [17, 23, 29].

The clinical course of PU. On mature reflection, we decided to abandon the detailed presentation of the clinical picture of ulcer, since it is well known to doctors. We mention briefly the symptomatology of PU, but for another reason.

Proponents of the concept of the leading role of Hp in the etiology and pathogenesis of PU, after the possibility of developing the disease was proved without any involvement of Hp (Hp is a negative form of PU), it seems that in order to “save face”, they proposed to divide the single nosological form for 3 independent diseases:

1. Hp-associated PU.

2. Idiopathic ulcer.

3. PU caused by taking nonsteroidal anti-inflammatory drugs — NSAIDs [7, p. 127; 13].

This absurd proposal to isolate Hp-associated PU from idiopathic ulcer (with unknown etiology) pursued a single goal: to artificially bring it into compliance with one of the three requirements of the Koch Triad: “The pathogen microbe must always be found in the patient’s body” (in this case, when PU) and wrong postulate by D.Y. Graham "No Hp — No PU".

With regard to erosions and ulcers formed in the stomach and duodenum during chronic administration of NSAIDs, — [it is generally not PU and symptomatic (secondary) erosion and ulcer drugs with known etiologies (NSAIDs) 19, 22, 32].

Idiopathic ulcer is known to be characterized by a chronic course with a change of relapses and remissions; the formation of a single ulcerative defect, usually localized more often in the duodenum than in the stomach [22, 23].

At the same time erosive-ulcerative damage in gastroduodenal zone while taking NSAIDs are distinguished from PU formation of multiple erosions and ulcers, often in antral compartment of the stomach than in the duodenum, and have permanent (continuous) progressive course [32].

Finally, the so-called (so-called) Hp-associated ulcer, as follows from the irrefutable scientific facts and arguments presented by us, is not associated with gastric contamination by Hp infection, as its etiological factor, and, therefore, should also be attributed to the idiopatic ulcer [21, 22, 23].

Treatment of PU. The basis of therapeutic interventions for PU still (alas!) Put an erroneous theory (the concept of) the leading role of Hp in its origin shall be considered PU, as a local pathological process caused bakter ialnoy infection (Hp) and acidosis peptic aggression. Expression of this erroneous concept is another postulate D. The Y. Graham : “PU should be considered as a local manifestation of a bacterial infection (Hp)” [22]. At the same time, the systemic nature of the disease is completely ignored, and all patients are offered standard treatment. Drugs that inhibit acid formation in the stomach (proton pump inhibitors — PPI), and a complex of antibacterial agents for eradication of Hp. The well-known principle of domestic medicine about the need for individualization of treatment is not taken into account (G.A. Zakharyin: “The main rule in prescribing treatment... is the observance of the method of individualization” [6].

Group of the European gastroenterologista headed by R. Malfentheiner (Germany), since 1997, publishes its recommendations on the diagnosis and treatment standards for diseases associated with Hp-infection known as the "Maastricht consensus". Over the past 20 years, 5 such recommendations have been published (MC–1–5), which are updated approximately 1 time in 4 years.

I. For the eradication of Hp infections all the time, the same drugs are recommended, in essence: as antacid agents, proton pump inhibitors — PPI (omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole) are mainly used, and for destruction (eradication)) Hp — antibacterial agents (clarithromycin, amoxicillin, metronidazole and de-nol — bismuth sulfate or subsalicylate). The "MC–4" (2010) in connection with increasing every year Hp resistance to those used for their eradication antibacterial agents has been proposed backup antibiotic — levofloksatsin, and to recover repressed antibiotics endosymbiotic intestinal microflora — probiotics and synbiotics [16, 43].

Nevertheless, the resistance of Hp and other bacteria colonizing the stomach to the antibacterial agents used continues to

grow and has already reached a critical level. Thus, the resistance of Hp to clarithromycin varies from 23.1 to 36.1%; amoxycillin — from 26 to 36.3% ; to metronidazole — from 40.7 to 65% [9, 11, 45]. Antibiotic resistance genes are found in plasmids, the reservoir of which is the intestinal microbiota [7].

It seems to us that the main reason for the steadily growing resistance of Hp to treatment is the miscalculations of the authors-compilers of “MC”, who monopolized the right to determine the indications and methods of eradication therapy, proclaiming a strategy for total destruction of Hp- infection (test and treat strategy : identify and eliminate!) [43].

I. The indications for eradication of Hp were unreasonably expanded due to patients with gastroesophageal reflux disease (GERD); with the syndrome of functional (gastroduodenal) dyspepsia (SFD); before starting a course of treatment for NSAIDs (patients with rheumatoid arthritis, etc.) and even healthy bacteria carriers (“at the request of the patient”) And this is despite the evidence that the development of these diseases is not associated with Hp infection. The authors of the compilers themselves were forced in "MC — 4" (2010) to recognize:

1. "Hp does not affect the severity, frequency of symptoms, and the effectiveness of treatment for GERD, and epidemiological studies show a negative correlation between the spread of Hp and the development of GERD and esophageal adenocarcinoma." In other words, after eradication of Hp, the frequency of GERD and adenocarcinoma of the esophagus increases (1.5 — 2 times).

2. "In the syndrome of functional dyspepsia, eradication of Hp causes complete and prolonged elimination of symptoms in 1 of 12 patients" (which amounted to 8.3%). And according to the "Rome criteria", the use of placebo for SFD is effectively 20–40% or more!

3. “Eradication of Hr ne does not eliminate the risk of ulcer formation while taking NSAIDs” [13, 32]. Comments, as they say, irrelevant... As regards the recommendation to conduct Hp eradication in healthy-bacteria carriers — "on the patient’s

wishes," we believe that the decision to place the question of holding the course of eradication therapy on people with no medical training, is unacceptable [16, 43].

II. Compilers "MC" artificially set a low line of efficiency undertaken eradication — %, allowing the survival of up to 20% of Hp. But it is obvious that resistance to the action of the used antibacterial agents, and after the destruction of sensitive to them pieces of Hp strains, will give offspring immune to the treatment being carried out!

III. The authors' commitment of "MC" over the course of 20 years to the same antibacterial drug also contributes to the spread of resistant Hp strains [21, 22, 23].

We believe that consensus (conciliation meeting) contradicts the basic principles of evidence-based medicine, since they do not include the use of such important elements of knowledge as the logic of clinical thinking, analysis and synthesis (synthesis) of factual data, etc. thinking independently by a researcher, and a simple technical executor of the proposed recommendations, which fundamentally contradicts the basic principles of medical practice [21, 23].

We believe that the treatment of recurrent PU, as a systemic disease, should be complex and individualized with the impact on the various pathogenesis stages that were listed earlier, and do not accept the standard treatment that is common for all patients with PU, affecting exclusively local factors of pathogenesis — acidopeptic (HCI) and infectious (Hp).

1. We include nootropil (piracetam), which has a combination of psycho-, neuro- and somatotropic effects, which contributes to the normalization of the gastroduodenal functional regulation system in the complex of therapeutic measures in the treatment of recurrent ulcer. When the nootropil complexed with the "triple circuit" Hp eradication and other microbiota colonizing the stomach (API + clarithromycin — 500 mg amoksitsillin — 1000 mg) in 3 weeks marked scarring ulcers in 93.5% of patients (the control — in 75.5% ; $p < 0.05$), and the number of recurrences of

ulcer in the first year after the course of treatment with the inclusion of nootropil is reduced to 5% (in the control — 18.9% ; $p < 0.05$) [34].

Dose of nootropil: 400 mg 3 times/day within 3-4 weeks. As our studies have shown, nootropil has a positive effect on the integrative activity of the brain and the processes of information transfer, restoring management and control mechanisms. The main pharmacological effects of nootropil are: neuroregulatory, neurodynamic, neuroan bolic and eutrophic [33, 34].

2. When identifying in patients with PU, psychopathological disorders of a neurotic level with a depressive (76%) or hypochondriac component resulting from a psycho-traumatic effect, and also in the presence of emotional disadaptation, anxiety with subsequent somatic disorders, we prescribed cipromil (citalopram) — a balanced antidepressant, also having anxiolytic (anti-disturbing) and adaptation effects. Dose: 20 mg/day. within 4 to 6 weeks.

In addition, we used the methods of gestalt psychotherapy in these patients, which ensures the elimination of neurotic disorders, the improvement of the quality of life and the achievement of personal compensation [25, 26]. For the gestalt psychotherapy sessions, we invited a psychotherapist.

3. Development PU and its relapses may depend as well on the condition of the immune system, — presence immunodeficiency syndrome flowing as a combined lesions of all parts of the immune system, particularly the T-cell link.

In these cases, the effect is achieved by administering immuno-modulating agents. We used imunofan in d Oz 1 ml of 0.005% solution intramuscularly (10 injections) alternating with taktivin (1 ml of 0.01% solution under the skin, 10 injections) and in conjunction with the reception of oligovit (complex of vitamins and trace elements — 1 tablet in the evening — before bedtime).

The combined use of the “triple scheme” of Hp eradication in combination with immunomodulators increased the Hp eradication effect from 55 to 84% ($p < 0.05$) and reduced the number of

recurrences of ulcer cancer from 33.6 — 42.1 to 12.5% during the year ($p < 0.05$) [30].

4. To reduce the activity of SRLO processes and improve regional blood flow in the stomach wall, we used natural antioxidant — sea buckthorn oil (BO), which includes: carotene-A (provitamin A), carotenoids (alpha, beta and gamma-carotene), lycopene and its derivatives, the sum of tocopherols (vitamin E) and glycerides (oleic, linolenic, palmetinic and stearic acid). Dose MO: 1 dess. spoon 3 times/day for 30 minutes. before meals; The course of treatment is 20-25 days.

According to our data, the course of treatment of BO reliably reduces the initially excessive activity of SRLO processes and increases the effect of antioxidant systems. In addition, it restores impaired hemodynamics in the wall of the stomach, reducing increased vascular tone, increasing the flow of arterial blood and reducing venous congestion [18].

Modern possibilities of drug effects on genetically-constitutionality l nye factor in the pathogenesis of PU minimal.

Concluding the article on the current state of the doctrine about PU, it should be noted that the origin of PU (its etiology) remains unknown.

This largely mysterious, peculiar disease (morbus sui generis) requires further comprehensive study and scientific substantiation of new, more effective therapeutic agents used to treat it.

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Peptic ulcer disease: a critical analysis of the current state of the problem

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Key words: peptic ulcer, history of research, Helicobacter pylori, pathogenesis, clinical picture, treatment

History of study of peptic ulcer, evolution of ideas about its etiology and pathogenesis are set out in this review. The preceding theories of the formation of peptic ulcer and the current provisions explaining the development of this disease are described. Special attention is paid to the role of the bacterium Helicobacter pyloput forwardri in the occurrence of peptic ulcer and the formation of its recurrence; the microbiological and genetic features of helicobacteria are described in detail, giving them unique pathogenic properties. The genetic, immune, psychogenic mechanisms of the pathogenesis of peptic ulcer are described, the significance of oxidative stress and local factors in the formation of the ulcerative defect of the mucous membrane is revealed. A thorough critical analysis of some of the provisions of the dominant theory of ulcerogenesis is carried out. The inconsistency of helicobacteria, which are considered the main etiological factor of peptic ulcer, to the requirements of the Koch Triad, is emphasized: this pathogen does not always provoke the development of erosive-ulcerative mucosal lesions and is frequently not detected in many patients with peptic ulcer. Own data illustrating the dysbiotic nature of the violation of the microbial landscape of the stomach, and not the prevalence of helicobacteria in patients with peptic ulcer, are presented. Clinical features of peptic ulcer disease are properly described. Statements of the Maastricht consensus are strongly criticized for contradicting the basic principles of evidence-based medicine and not allowing the use of clinical thinking, analysis and synthesis of evidence. There is a doubt about

the feasibility of the eradication of helicobacteria using the systemic broad-spectrum antibiotics. The rationale for further comprehensive study of peptic ulcer and the development of new, more effective therapeutic agents is put forward.